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ABSTRACT

Nutritional anemia is believed to be the most widespread nutritional disorder in the world. While it generally affects developing countries, developed countries are also affected to an extent sufficient to justify the implementation of preventive measures at a national level. This report focuses on iron and folate deficiencies, which are by far the most frequent causes of nutritional anemias. The discussion includes descriptions of iron and folate metabolism, consequences of deficiencies, methods of evaluation of iron and folate status, and prevention measures. A technical note on recommended iron intake takes into account bioavailability in dietary regimens around the world. The report also includes a statement released by the International Vitamin A Consultative Group on the role of vitamin A in child health and survival and a report of studies of iron absorption from meals including maize flour products that are eaten by Venezuelan adults. Of all human nutritional requirements, the requirement for iron raises the greatest practical problems. But thanks to increased epidemiological understanding, improved preventive measures can be implemented and their impact evaluated with increased accuracy. A chart provides basic and preventive estimated dietary iron requirements by sex, age, reproductive status of women, and for diets with low, moderate, and high bioavailability. (RH)

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IRON AND FOLATE - DEFICIENCY ANAEMIAS

1990 - N° 186

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INTERNATIONAL CHILDREN'S CENTRE – PARIS

The International Children's Centre was created by the French government in 1949, on the initiative of Professor Robert Debré in particular, following negociations between France and the United Nations. Its purpose was to furnish those international and national agencies dealing specifically with child care with training facilities and educational and informational tools in the field of child health and development, viewing children within their family and surroundings.

ICC soon turned essentially toward Third World children and devoted its activities to the training and education of personnel with social, educational and administrative responsabilities as well as medical and paramedical workers. The desire for greater efficiency has led it to work increasingly with trainers and to concentrate its efforts on the methodological and educational aspects of mother and child care programmes.

ICC is also engaged in an attempt to further study — and — action on some aspects of the life and health of children and their family, so as to contribute to practical improvement, particularly in the fields of growth, nutrition, planned parenthood, the control of transmissible and nutritional diseases, preschool and school education, the needs of disabled and underprivileged children, etc.

Over this period of more than 30 years, a large amount of documents on children and adolescents, mostly from the developing countries, has been accumulated. This international documentation has been classified and sorted out, and has been computerized since 1983 : a bibliographic data base (BIRD : « Base d'Informations Robert Debré ») may be consulted anywhere in the world, through international communications networks. ICC also publishes periodicals, educational documents and specialized bibliographic bulletins.

As for its legal status, the International Children's Centre is a foundation under french law of recognized public utility, administered by an executive board with broad international membership.

Our cover : « LAS HERMANAS » - Watercolour, painted by the Ecuadoran Oswaldo GUAYASAMIN - Quito, Ecuador, 1942.

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CHILDREN
IN THE TROPICS

REVIEW OF THE INTERNATIONAL CHILDREN'S CENTRE

IRON AND FOLATE-DEFICIENCY ANAEMIAS

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1990 - N° 186

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IRON AND FOLATE-DEFICIENCY ANAEMIAS

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IRON AND FOLATE-DEFICIENCY ANAEMIAS

Nutritional anaemia is believed to be the most widespread nutritional disorder in the world. While it essentially affects developing countries, industrially developed countries are also touched, to an extent which, although lesser, has been judged sufficient to justify the implementation of prevention measures at a national level. According to the World Health Organization, 500 million to 1 billion individuals, representing 15 to 20 % of the world population, are presently affected by this condition.

Despite an abundance of epidemiological, clinical, biological and experimental information, the various types of nutritional anaemia still represent a major problem for many countries around the world, owing to its detrimental effects on both individual health and community life. For the proper comprehension of the nature and causes of nutritional anaemia, the distribution of its different forms within population groups and the consequences in terms of public health, as well as for an examination of the best levels for enacting possible preventive measures, it is most important to achieve an accurate understanding of the pathophysiological bases involved in the metabolism of those nutrients that play a role in the synthesis of haemoglobin, as well as of the gender and age-related modifications in requirements, and of those linked with different physiological circumstances.

This study only deals with iron and folate-deficiency nutritional anaemias, which are by far the most frequent aetiologies in nutritional anaemia world wide.

NUTRITIONAL ANAEMIA

THE GENERAL MECHANISM

In healthy individuals with a satisfactory nutritional status, there is an equilibrium : for each and every nutrient, the amount absorbed from the diet must suffice to cover needs for that nutrient ; that is, it must ensure its metabolic use by the body, compensate for losses and maintain adequate reserves. This nutritional equilibrium may be thrown off balance by insufficient intake or absorption of the nutrient, and/or by increased needs or losses.

When the equilibrium is disrupted for any one or a combination of these reasons (which may of course combine and be mutually potentiating), the outcome is a deficiency situation for the nutrient involved. When faced with this situation, the body initially uses its reserves. When these reserves are exhausted (and perhaps even before the reserves are totally depleted), all of the functions in which the nutrient is active will be disturbed. In the case of the haematopoietic nutrients, there is a drop in the synthesis of haemoglobin, leading to anaemia.

DEFINITION

According to the WHO definition, the term "nutritional anaemia" encompasses all pathological conditions in which the blood haemoglobin concentration drops to an abnormally low level owing to a deficiency in one or several essential nutrients, regardless of the cause of this deficiency.

Given the existence of an individualized mechanism regulating the synthesis of haemoglobin, it is not easy to define "normal" values for haemoglobin, and the limits beyond which the concentration may be said to be "abnormally low". However, WHO has defined indicative cut-off points which may serve as guides for the definition of anaemia at both the individual and the community levels (table 1).

Table 1

CUT-OFF POINTS DEFINING ANAEMIA (AT SEA LEVEL), ACCORDING TO WHO

Children age 6 months to 6 years	11 g/100 ml
Children age 6 years to 14 years	12 g/100 ml
Male adults	13 g/100 ml
Female adults (from puberty to menopause)	12 g/100 ml
Pregnant women	11 g/100 ml

Superior cut-off values are set for individuals living at high altitudes : a correction of 0.4 g/dl per additional 1,000 m of altitude (beyond 1,000 m) is generally used to adjust reference cut-off points.

THE HAEMATOPOIETIC NUTRIENTS

The main nutrients involved in the synthesis of haemoglobin are iron, folic acid and vitamin B12. Other minerals (copper, zinc, magnesium, cobalt and molybdene) and certain amino acids seem to play a role in the maturation of red cells and in the synthesis of

haemoglobin in animals, but there is no definite proof of their role in humans.

In public health terms, iron deficiency is by far the first cause of nutritional anaemia world wide. Folic acid deficiency is less widespread and is in fact often observed in conjunction with iron deficiency. Vitamin B12 deficiency is far more rare.

EPIDEMIOLOGY

Although most of the epidemiological surveys conducted over the last 3 decades were limited ones, they do provide some notion of the geographic distribution of nutritional anaemia :

— in Africa, its prevalence (1) (South African Bantoos excepted) may be estimated at 6 to 17 % for men, 15 to 50 % for women and 30 to 60 % for children under 14 ;

— in Asia, 10 % of men and 30 to 50 % of women are affected by nutritional anaemia. Figures of 80 to 90 % are frequently reported in India, Pakistan and Bangladesh, among pregnant women. The prevalence is somewhere around 50 % for children, and may exceed 90 % for children under 2 years old in certain studies ;

— in South America, frequency figures range from 5 to 15 % for men and from 10 to 35 % for women and exceed 50 % for pregnant women. Most studies indicate a 15 to 50 % range for the percentage of anaemic children ;

— in Oceania, in studies conducted in the South Sea Islands, over 70 % of the women seen were found to be anaemic ;

— in the industrialized countries, studies done in North America and Scandinavia show that 1 to 6 % of women of childbearing age and 1 to 2 % of adult men are anaemic. In France, 2 to 3 % of the women of childbearing age studied, 10 % of children under 2 and 10 to 25 % of pregnant women are anaemic.

In all, epidemiological findings indicate the enormous extent of the problem, globally, with the developing countries being most affected. It should immediately be made clear that the existence of nutritional anaemia is indicative of an advanced stage of deficiency (in iron and/or folates) ; consequently, the prevalence figures for more moderate degrees of these deficiencies (before they affect haematopoiesis) (2) are most certainly much higher than would be indicated by findings based entirely on the evaluation of the

(1) Prevalence : the total number of cases of a disease in a population group at a given time (immediate prevalence) or during a given period of time, regardless of the onset of the illness and with no differentiation of new and old cases, in proportion to the entire group observed.

(2) The haematopoietic organs : in adults, the bone marrow, lymph glands and spleen are the main haematopoietic organs. In the embryo and the foetus, these organs are the islets of Wolff during the first two months, the liver until the 5th month and the spleen until the last month of intrauterine life. Haematopoiesis is the whole series of cell processes occurring in the haematopoietic organs and yielding all of the blood constituents (red cells, white cells, etc).

frequency of cases of anaemia. Regardless of the country or the continent, whatever the level of development, it is evident that women of childbearing age, pregnant women and children (especially during the rapid growth period) represent at-risk groups for nutritional anaemia. These epidemiological findings may be clearly explained by the peculiarities of the metabolism of haematopoietic nutrients, and more specifically, of iron and folic acid.

IRON DEFICIENCY

THE METABOLISM OF IRON

Distribution and role of iron

Although it is present in the body in extremely small amounts - approximately 2.5 g in women and 4 g in men (representing 0.005 % of body weight) - haeme and non-haeme forms of iron are active in several parts of the body and in many metabolic functions.

Haeme iron : this is the iron which participates in the structure of haeme (1). Haeme is composed of a tetrapyrrolic nucleus (protoporphyrin) and an atom of ferrous iron. Thus, haemoglobin is composed of four sub-units, each containing haeme and a protein portion, or globin. Haemoglobin is the main intracellular protein composing red blood cells : it carries oxygen from the lungs where it is held, to the tissues where it is released. It carries between 700 to 1,000 litres of oxygen per 24 hours.

Myoglobin only contains a single haeme, which is the same as in haemoglobin. It represents the respiratory pigment of muscles, and its function is the storage and circulation of oxygen within the muscles. Haeme iron also participates in the composition and activity of many enzymes that play a major role in the mechanisms involved in electron transport at the cellular level, thus controlling many metabolic functions (catalase, peroxydase, cytochromes). These haemoproteins contain from one to four atoms of iron.

Non-haeme iron : non-haeme iron is also present in many enzymes (succino-dehydrogenase, phenylananine hydrolase, xantine oxidase...), generally in a covalent form. It is also in the non-haeme form that iron is transported in the plasma and stored in the body.

Storage iron is confined in a specific protein, called ferritin. The iron contained in ferritin is readily available, and easily mobilized in case of need, particularly for the synthesis of haemoglobin and the maintenance of various cellular functions (enzymes, myoglobin...). Most body tissues contain small stores of iron, but the main organs in which iron is stored are the liver, spleen and bone marrow. When the body's iron reserves are large, the amount of intracellular ferritin rises, forming aggregates. The resulting iron complexes constitute haemosiderin, the mobilization of which is much more difficult.

For transportation, iron is bound to a protein of hepatic origin, transferrin or siderophilin, in the plasma. In normal individuals, this protein is only partially saturated - to about 30 %. The main role of transferrin is to carry iron to the tissues in which it is needed, and above all to the erythropoietic apparatus. It also serves to recover the iron released by the breakdown of haemoglobin during the haemolysis of red corpuscles (the life span of which is 120 days). It also seems to have a bacteriostatic function. Some other proteins

(1) Haeme : haeme is one component of haemoglobin ; it is composed of protoporphyrin, with one atom of metal iron in a ferrous state, which may bind oxygen. Globin constitutes another portion of haemoglobin.

- lactoferrin, ferritin - are capable of transporting iron, but they apparently are not active in the physiological transport of iron.

The main originality of iron metabolism resides in the fact that it occurs practically within a closed circuit : the body is particularly thrifty of its iron. In human beings, the amounts of iron eliminated daily (which theoretically should be covered by iron intake) are somewhere between 1 and 2 mg a day ; this only represents a minute portion - 1/2,500th to 1/4,000th - of the body's total pool of iron. Nonetheless, this slight dependency on intake is an extremely important factor in the overall equilibrium of the system. If losses are not compensated by intakes, there is in fact a risk of developing deficiency.

A proper understanding of the mechanisms by which non-coverage of iron requirements leads to deficiency requires an overview of the way in which loss of iron occurs within the body, as well as of dietary intake and of the factors that may play a role in balancing out intakes and losses of iron.

Losses of iron

In adults, 0.2 to 0.3 mg of iron are lost daily through desquamation of the skin, about 0.1 mg in urine, 0.6 mg in faecal excretion (including only 0.14 mg of iron originating in the bile, the rest coming from gastrointestinal desquamation). Average basal losses are estimated at 12-14 µg of iron/kg/day, representing 0.9 to 1 mg/day in adult men and 0.7 to 0.8 mg/day in adult women, given their respective average weights. From puberty to menopause, women experience further losses of iron resulting from menstrual bleeding.

Much research has been devoted to the assessment of the extent of menstrual losses in women of varying geographic origins. All of these studies, comparing menstrual losses during consecutive periods, have shown blood losses to be constant from one cycle to the next for a same woman, while there are extremely marked inter-woman differences. Various investigations conducted in Sweden, Great Britain, India, Burma and Egypt on apparently healthy women resulted in comparable findings : medians (1) for menstrual blood losses range from 20 to 30 ml/month, representing a loss of about 12 to 15 mg of iron per month, or 0.4 to 0.5 mg a day. These losses are of course incremental to the other basal physiological losses. While intra-individual variations are slight, inter-individual variations are considerable. 10 % of women otherwise considered to be healthy evacuate more than 80 ml of menstrual blood each month, resulting in an additional iron depletion of about 1 mg/day. Numerous factors such as weight, height and parity influence the volume of menses. One major factor is the utilization of certain types of contraception. Oral contraceptives may decrease the menstrual volume by 50 %, whereas an increase of more than 100 % is observed in women equipped with an intrauterine device.

(1) Median : that value of a variable which divides the entire set of values into two equal halves.

Since physiological iron losses are increased by menstrual losses, women are obviously exposed to a greater risk of iron deficiency between puberty and menopause.

Abnormal losses - especially slight but repeated ones - may exacerbate the "usual" physiological losses. Causes of those include digestive cancers, hemorrhoids, repeated intake of medications which may cause micro-bleeding (aspirin, anticoagulants...). In tropical regions, digestive parasitoses, and more particularly ancylostomiasis (600 to 700 million people are infested with ancylostomas, according to WHO) are the most frequent causes of abnormal losses of iron : daily blood losses may represent 2 to 100 ml depending on the severity of infestation, and may rob patients of considerable quantities of iron. In cases of infestation by Nector americanus, about 0.03 ml of blood is lost daily per worm, or approximately 2 ml for a load of 1,000 eggs per gramme of stools. Despite the partial reabsorption of haeme iron, total daily losses may be as high as 0.8 mg of iron when the accumulation is considerable. In the case of duodenal Ancylostomas, an estimated 0.2 ml of blood is lost per day and per worm, for a total of 4.5 ml for a load of 1,000 eggs per gramme of faeces ; this represents an additional daily iron loss of about 1.8 mg. Trichuris trichiura may also induce intestinal bleeding of about 0.25 mg/day in the case of massive parasite infestation. Urogenital schistosomiasis may also cause depletion during the infestation period, through haematuria, which often disturbs the iron balance.

The presence of parasitosis (a frequent occurrence in tropical areas when infestation is rampant) is a compounding factor, interacting with other risk factors, for the development of iron deficiency.

Specific needs

In pregnant women

Iron requirements are considerably increased during pregnancy. Iron is needed not only to compensate the usual losses (urine, faeces, cutaneous desquamation...) but also to cover the woman's increased erythrocyte volume and the needs connected with foetal and placental growth.

In a well-nourished woman, there is an increase of about 500 mg in the blood mass and the number of red blood corpuscles ; this iron is recovered following delivery. The at-term foetus contains approximately 290 mg of iron and the placenta another 25 mg. The expectant mother's usual physiological losses through the faeces, urine and perspiration are not modified ; 0.8 to 1 mg per day, or approximately 240 mg for the entire gestation period (table 2). The absence of menstruation during pregnancy "economizes" some iron, but not enough to compensate for the major increase in needs entailed by pregnancy, which are frequently compounded by losses of iron through bleeding during delivery and the post partum period (about 250 mg, and even more when complications occur during delivery).

Table 2

AVERAGE IRON REQUIREMENTS DURING PREGNANCY

	1st trimester	2nd trimester	3rd trimester	TOTAL
Increase in erythrocyte volume	--	250	250	500
Foetal iron	--	60	230	290
Placenta iron	--	--	25	25
Bleeding during delivery and post partum	--	--	--	--
Physiological losses	80	80	80	240
TOTAL	80	390	585	1 055

In all, 1.055 mg of iron are required in response to the various pregnancy-related expenditures : this represents an extremely large amount.

Studies measuring iron absorption in pregnant women have discovered a gradual increase in capacity of absorption, particularly during the second half of pregnancy (as the woman's iron stores dwindle). However, this compensatory mechanism generally does not suffice to make up for the considerable increase in needs connected with gestation, whence the risk of iron deficiency and anaemia in pregnant women. Multiparity and small birth intervals take a toll on women's ability to build up new reserves, and thus constitute further risk factors. The concept of "physiological gestational anaemia", a long-consecrated notion, was generated by the observation of a high frequency of anaemia during gestation. Studies of iron supplementation have shown that haemodilution (taken into account by the WHO definition of the cut-off point for gestational anaemia) is not a sufficient explanation of the declining haemoglobin concentration during gestation. Anaemia may be treated or avoided by iron supplementation.

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In neonates, infants and children

Children need iron in order to cover their basal needs, and to cope with the expansion of their erythrocyte volume and the rapid growth of body tissues. The body of an at-term neonate born to a healthy mother contains approximately 290 mg of iron, 3/4 of which is located in the circulating haemoglobin ; it has a high serum haemoglobin concentration, comprised between 16 and 20 g/dl. At age 1 year, the same child possesses about 400 mg of iron. During the first 4 to 6 months of life, the iron contained in the haemoglobin is redistributed to the growing tissues, so that needs may be met. Beyond the 5th or 6th month, the infant's iron reserves are depleted, even in the most favourable cases, when the child is breast-fed, whereas needs are considerable : there is therefore an obvious risk of deficiency. Low birth weight neonates

(prematures, twins...) have even lower iron reserves, and greater needs, and are even more exposed to the risk of deficiency (table 3).

There is also a great need for iron during childhood and adolescence (periods of rapid growth).

Physiological needs vary enormously with age and sex. These needs are increased in case of additional losses caused by pathological conditions.

Iron intakes

The body must draw a sufficient amount of iron from its diet to compensate for the iron it loses. Many foods contain iron in variable proportions. However, the actual intake of iron - that is, the amount that is really absorbed and is utilizable by the body - depends on the bioavailability of the dietary iron and on the individual's iron status, as well as on the iron content of food.

The iron content of food

This varies from one food to another. Cereals, roots, tubers, vegetables and leaves are poor in iron. The iron content of meat, eggs and fish is moderate, with the exception of organ

Table 3

BASIS FOR CALCULATING ADDITIONAL REQUIREMENTS OF ABSORBED IRON FOR GROWTH (1)

Group	Age	Weight gain (kg)[2]	mg of iron/kg of body weigth				Average iron requirements for growth (mg/day)[6]
			Haemoglobin[3]	Myoglobin[4]	Enzymes[5]	Total	
Infants	3-12 months	4.2	32	3	2	37	0.65
Children	1-2 months	2.4	32	3	2	37	0.24
	2-6 months	7.9	32	6	2	40	0.22
	6-12 months	20.2	33	6	2	41	0.38
Boys	12-16 months	26.2	37	7	2	46	0.66
Girls	12-16 months	15.2	34	7	2	43	0.36
Adult men		—	39	7	2	48	—
Adult women		—	34	7	2	43	—

(1) Method: To calculate weight gain within each age group, the weight at the lowest age is substracted from the weight at the highest age. This weight increment, expressed in kg, is multiplied by the amount of non-stored iron in the body, per kg of weight, for each age group, on the basis of the data described in notes (3) to (5), hereunder. The product, which represents the amount of iron required for growth over the entire period, is then divided by the number of days included in the age period ; this shows the total amount of iron required daily for growth.

(2) Weight gains are taken from the WHO tables of growth.

(3) Calculations of non-stored iron per kg of weight are based on the following data : haemoglobin concentration, using the median reference values for the United States, except for children under 2 years, for whom the values are taken from another reference group ; the blood volume is assumed to be 75 ml/kg ; 1 g of haemoglobin contains 3.4 mg of iron.

(4) To calculate the amount of iron present in myoglobin, a myoglobin concentration of 5 mg/g of muscle in children over 2 years of age, on the basis of values recorded in adults, and of 3.5 mg/g of muscle in infants, is assumed. The proportion of muscle to body weight is estimated on the basis of the accepted references ; 1 g of myglobin contains 3.4 mg of iron.

(5) The iron content of enzymes is estimated at approximately 2 mg/kg of body weight.

(6) To the exclusion of storage iron.

Taken from FAO/WHO. Vitamin A, iron, folic acid and vitamin B12 requirements. FAO collection : Food and nutrition. Rome, 1989. N 23. 119 p.

meat which is very rich in iron. Dried legumes contain the largest amounts of iron (table 4).

Table 4

IRON CONTENT OF FOODS

Foods	Iron content mg/100 g	Food	Iron content mg/100 g
Sugar	0	Pineapple	0.4
White bread	0.4 - 0.8	Avocado	1.4
Wheat (flour)	2.2 - 3.6	Strawberries	0.7
Maize (flour)	3.0 - 3.4	Guava	1.3
Millet (flour)	2.0 - 3.3	Mango	1.2
Teff (flour)	14.9 - 105.0	Orange	0.1
Sorghum (flour)	8.6 - 10.0	Grapes	0.8 - 2.1
Brown rice	0.5 - 2.0	Papaya	0.6
Polished white rice	0.3 - 1.7	Mutton	1.5 - 2.5
Plantain banana	1.3	Beef	2.9 - 5.6
Yams	0.8 - 1.6	Beef heart	4.0
Manioc	0.7 - 1.9	Pork	1.5 - 2.3
Sweet potatoes	0.2 - 5.7	Chicken	1.1 - 2.0
Potatoes	0.8 - 1.1	Organ meat	8.0 - 18.0
Groundnuts	3.8	Chicken egg	2.0 - 2.6
Beans	1.4 - 9.6	Oyster	6.0 - 7.0
Lentils	7.0	Pike	0.8
Cowpeas (Niebe)	7.6	Nile perch	4.1
Chick peas	11.2	Sea bream	1.4
Soybean (flour)	6.0	Mackerel	1.2
Baobab (dried leaves)	24.0	Sardine	1.3
Carotts	0.7	Tilapia	0.4
Spinach	1.7 - 4.4	Tilapia	3.2
Laitucce	1.0	Cow's milk	0.03 - 0.05
Okra	1.2	Breast milk	0.07 - 0.15
Marrows	2.8	Butter	0.2
Tomatoes	0.6	Chocolate	1.6 - 2.4
Red peppers	2.9	Wine	5.0 - 25.0

Certain tables of food composition show high iron content figures for a number of foodstuffs including cereals (millet, sorghum and teff). Much of this iron is the result of "contamination" by environmental sources (dust during drying, additions during processing, etc). It is not a part of the natural iron content of the food. The quality of this iron added by "contamination" does not ensure its proper absorption by the intestine.

Bioavailability of dietary iron

The decisive factor for coverage of needs is the nature of the iron present in food, even more than the total quantity present. Various studies using foods labelled with radioactive iron (Fe 55, Fe 59) have in fact discovered that the average iron absorption of healthy individuals is extremely variable from one food to another, ranging from 1 to 5 % for foods of plant origin and from 10 to 25 % for meat and fish. These differences are explained by the type of iron - haeme or non-haeme - contained in these foods.

Haeme iron is only present in some foods of animal origin, either meat or fish, in which it represents approximately half of the total iron. The other foods of animal origin (eggs, milk and dairy products) do not contain any haeme iron. Non-haeme iron exists in foods of both animal and plant origin. Haeme iron is much more easily absorbed than non-haeme iron : its coefficient of absorption is somewhere around 25 %, whereas no more than 5 % of non-haeme iron is absorbed.

This makes it possible to calculate the overall coefficient of iron absorption for each food (1 to 2 % for rice, 3 to 4 % for dried legumes, 16 to 22 % for meat, 50 to 70 % for breast milk...). However, these coefficients of absorption, calculated on the basis of the consumption of each food taken separately, are of only theoretical value, since there are numerous interactions between different foods eaten in the course of a same meal : certain substances present in food tend to facilitate the absorption of the iron contained in the ration, whereas others act as inhibitors of that same absorption. It is only the absorption of non-haeme iron (the main source of dietary iron in developing countries) which is affected by the composition of the meal.

Activators of iron absorption

Ascorbic acid is the most powerful known facilitator of the absorption of non-haeme iron. The absorption of the iron contained in a meal may be multiplied by 3 when 100 ml of fresh orange juice are added to the meal, and by 7 when 100 ml of papaya juice is consumed. The activating effect is enhanced by increased intake of vitamin C. Other acids such as citric acid, malic acid and tartaric acid, also present in fruit and particularly in citrus fruit, have an activating effect on the absorption of non-haeme iron as well.

In recent years meat and fish have been discovered to have a facilitating effect : the absorption of non-haeme iron is multiplied by 2 or 3 when proteins of animal origin (meat and fish only) are added to the meal. The action of 1 g of meat is approximately equivalent to that of 1 mg of ascorbic acid. The exact mechanism of this activating effect has not yet been completely elucidated.

Inhibitors of iron absorption

In 1975, tea was discovered to inhibit the absorption of iron ; a single cup of tea taken during a meal may cause iron absorption to drop from 11 % to 2.5 %. In a western-type breakfast, the absorption of non-haeme iron is reduced by about 60 % by the consumption of tea. By contrast, tannin-free tea does not affect the absorption of iron. The inhibitor effect of tannins resides in the generation of insoluble precipitates of iron tannates. Tea is the most powerful experimentally demonstrated inhibitor of iron known at present. Coffee also contains tannins, but it does not affect iron absorption as seriously as tea. This effect may also be connected with the presence of other polyphenolic components. Plants also frequently contain tannins, the presence of which may account for the poor absorption of the iron contained in this type of food.

Research has shown that the absorption of non-haeme iron in humans is considerably reduced by ingestion of egg yolk. This has been attributed to the action of vitellin, the main phosphoproteic complex contained in the yolk of eggs. Phosphate compounds

contained in a meal seem to inhibit iron absorption through the creation of nonsoluble ferric phosphate. This effect is apparently accrued by the simultaneous inclusion of calcium in the meal, which would then result in the co-precipitation of iron by a nonsoluble calcium-phosphate complex. Consumption of moderate quantities of milk does not seem to affect the absorption of non-haeme iron.

Phytates and fibre are suspected of inhibiting the absorption of non-haeme iron.

Future research on the bioavailability of dietary iron will most probably uncover many other activators and inhibitors, the understanding of which will yield improved estimation of the amount of iron actually biologically available from a given type of nutriture. This is especially important since the absorption of dietary iron may range from 1 to 20 % in individuals with similar iron stores, depending on the presence or absence of activating and inhibiting substances. This is an essential factor which must be taken into account if the overall problem of coverage of iron requirements is to be properly understood.

In all, three types of dietary patterns may be defined, grossly, with respect to absorption of dietary iron :

- diets containing iron with a "low bioavailability" (about 5 % absorbable) : this is the case of types of nutriture characterized by repetitious meals based on cereal and/or root and tuber staples, poor in foods of animal origin and in sources of vitamin C ;
- meals containing iron defined as having "relatively satisfactory bioavailability" (about 10 % absorbable). These meals are also based on cereal and/or root and tuber staples, but they contain some food of animal origin and some sources of vitamin C ;
- meals containing iron defined as having "high bioavailability" (about 15 % absorbable). These are varied, diversified diets containing large amounts of food of animal origin and with a high vitamin C content.

It is clear that most inhabitants of developing countries have diets of the first type, containing iron with low bioavailability. This helps to understand why the population of these countries is at greater risk of iron deficiency.

Individual iron status

Research has repeatedly demonstrated that the amount of dietary iron absorbed depends not only on the nature and amount of iron contained in food, but also on the state of the body's iron stores. Absorption of non-haeme iron is increased when the body's store of iron declines, and conversely, it drops when an iron overload occurs. However, this compensatory effect remains limited even in severely deficient individuals.

A technical note summarizes presently available data on recommended iron intakes, taking into account dietary regimens ; that is, the bioavailability of iron.

CONSEQUENCES OF IRON DEFICIENCY

The clinical picture typical of anaemia, with pallor and signs of suffering in those functional tissues and organs requiring large amounts of oxygen has been abundantly described in haematology and general medicine textbooks. The present description will be limited to the public health consequences of iron deficiency.

Repercussions on working capacity

Regardless of its aetiology, anaemia represents a major threat for tissue oxygenation, whence the possibility that certain functional tissues and organs that require much oxygen (the heart and brain) may suffer. The result is a diminished aptitude to perform energy-consuming tasks.

Studies conducted several years ago by Viteri and Torun (1974) in Guatemala on cane cutters provide outstanding evidence of the direct relationship between haemoglobin concentration and ability to perform physical exercise (measured objectively by the Harvard test), the latter being diminished by even moderate anaemia. Identical findings have been evidenced in workers collecting latex from heveas in Indonesia, and in tea harvesters in Sri Lanka. Productivity, measured by weight of the daily harvest, was significantly diminished in anaemic individuals. Following iron supplementation, the improvement in productivity paralleled the subsiding of anaemia, until it equalled that of non-anaemic workers.

Apparently iron deficiency itself, without anaemia, may play a role in reducing physical working capacity. Definite improvement of effort-requiring performances has been described following iron supplementation in deficient but non anaemic individuals, although their haemoglobin concentration was not significantly modified.

In laboratory testing, numerous enzyme and tissue impairments have been observed in the skeletal muscles of iron-deficient animals. Decreased alpha-glycerophosphate oxidase concentrations at the mitochondrial level have been described in deficient rats ; following iron supplementation, the activity of this enzyme increases as physical capacities are recovered, and prior to normalization of the haemoglobin concentration. Decreased alpha-glycophosphate oxidase activity seems to be the essential explanatory factor in the muscular disorders recorded in cases of iron deficiency. It apparently results in disturbed glycolysis, with the formation of excess lactate. High lactate levels would then cause reduced physical activity. In support of this hypothesis is the existence of high blood lactate concentrations in anaemic individuals following physical exertion : these levels tend to rise as haemoglobin values drop.

Other disturbances have also been described in the skeletal muscle of animals : decreased myoglobin concentration, decreased concentration of cytochrome c, and according to some authors, a decline in all cytochromes (iron-containing mitochondrial enzymes).

Repercussions on intellectual performance

Many symptoms such as apathy, somnolence, irritability, reduced attention span and inability to concentrate have been described during iron deficiency, even in the absence of anaemia. The subjective nature of these signs makes them difficult to interpret,

however, and there is no scientific demonstration, in human beings, of a causal relationship between iron deficiency and these disturbances, whose multifactoral character further complicates the evaluation of the specific involvement of iron deficiency. However, diminished academic performances have been evidenced in iron-deficient children, along with the reversibility of the phenomenon following supplementation with iron (in comparison with similar children who were given a placebo). This fact is particularly important since prevalence of iron deficiency is often high in this age group (up to 50 % of children, according to some reports).

A significant decrease in the activity of aldehyde oxidase, a key enzyme in the breakdown of serotonin and other 5-hydroxyindole compounds has been observed in the brain of iron-deficient rats. This results in a definite increase in serotonin concentration in cerebral tissues, which returns to normal following treatment with iron. This accumulation of serotonin in the cerebral tissue may induce certain symptoms of mental deterioration such as somnolence, reduced attention span, disturbance of intellectual abilities.

Some disturbances of mental activities attributed to iron deficiency in humans may also be the result of impairment of the monamine oxidase function. The activity of this enzyme is impaired both in vivo and in vitro in iron-deficient rats. This is corroborated by a significant decrease in platelet monamine oxidase (believed to accurately reflect the activity of this enzyme within the brain), demonstrated in subjects with iron-deficient anaemia. Monamine oxidase is an important enzyme for the catabolism of catecholamines ; any deterioration of its activity results in the excessive formation of catecholamines in the central nervous system. These seem to be the cause of certain anomalies occurring in individuals whose anaemia is due to iron deficiency, but not in those with anaemia of other origins. Such anomalies are in fact rapidly corrected by administration of iron.

Another interesting aspect of behavioural disorders is the occurrence, particularly in children and pregnant women, of "pica" or geophagism (an irresistable urge to eat earth) and pagophagism (the irresistable urge to eat ice). These are occasionally seen during iron-deficient anaemia, and disappear following treatment with iron (sometimes in conjunction with supplemental zinc), even before the anaemia is cured.

There is reason to believe, although this is difficult to demonstrate experimentally, that iron deficiency has a particularly powerful detrimental effect on the development of the brain during certain periods of extremely rapid growth of the brain and mental development (intrauterine period and early childhood).

Tissue impairment

Many tissue anomalies have been described in humans following iron deficiency. These include koilonychia (concave nails), commissural perleche, glossitis, atrophy of the gastric and oesophageal mucosa, the Plummer-Vinson syndrome (constriction of the upper oesophagus with risk of secondary carcinogenesis), etc.

These conditions seem to be linked with enzymatic disorders, since iron is either a component or a cofactor in many tissular enzymes.

Repercussions on immunity and infection

Strong controversies have arisen over the role of iron deficiency in immunity and host resistance to infection. Certain epidemiological investigations conducted in a number of industrialized or developing countries have uncovered a greater prevalence of infections in subjects suffering from iron-deficient anaemia, in comparison with non-deficient individuals. Conversely, other studies have observed iron supplementation to have a potentializing effect on infectious syndromes, but the interpretation of findings is very often thwarted by methodological problems (lack of a placebo group, comparison of non-comparable population groups, etc). There is some agreement, at present, on the negative role played by iron deficiency in immunity and individual ability to resist infections.

Iron deficiency induces impaired immunological defenses in both humans and animals. Lymphocyte transformation is anomalous, with diminished retarded hypersensitivity reactions (assessed by skin tests), neutrophile functions are impaired, etc. In iron-deficient animals, there is a marked disturbance of humoral responses, reduced leukocyte myeloperoxidase activity and increased sensitivity to the Escherichia coli enterotoxin.

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It is true that iron is also essential to bacterial growth, and greatly contributes to the pathogenicity and virulence of microorganisms. Some authors believe that iron deficiency may be a limiting factor in bacterial growth, and that the routine administration of iron to deficient subjects may constitute a factor of increased risk of infection. In fact, one decisive factor for the comprehension of the complex relations between iron status and infections is apparently the percentage of transferrin saturation. It is true that the growth of Esherichia Coli is inhibited by the addition of iron to a human plasma culture medium as long as the amounts added do not exceed the total iron-binding capacity. When the iron-binding protein (transferrin) is totally saturated, the excess iron is used for resumption of bacterial growth. The bacteriostatic and bactericidal action of lactoferrin has recently been emphasized ; the lactoferrin concentration in neutrophilic polymorphonuclear cells is lowered in iron-deficient individuals. Through its great iron-binding capacity, then this protein - like transferrin - seemingly prevents use of iron for the growth of microorganisms. Supplemental iron intake does not seem to be problematic, then, except in severely undernourished subjects affected with major disruption of the ability to synthesize transferrin. In such individuals, and in them exclusively, a massive intake of iron may exceed the total iron-binding capacity of their transferrin, and the surplus free iron may, in some cases, contribute to the growth of bacteria or parasites.

Repercussions on pregnancy

Anaemia is conventionally associated with a higher risk of prematurity and with increased foetomaternal morbidity and mortality. As early as 1961, Scott et al noted that neonatal mortality was multiplied by 20 for women with severe anaemia, as compared with a control group of non-deficient women. In 1963, Mac Gregor et al found that foetal mortality as well as prematurity are also linked with the severity of maternal anaemia : they are respectively 5.1 and 12.7 % when the maternal haemoglobin concentration is above 8.8 g/dl and 14.7 and 42 % when this concentration is below 7.4 g/dl. In India, a connection with anaemia was uncovered in 20 to 40 % of maternal deaths occurring at the Nagpur University hospital between 1955 and 1964. Conditions such as miscarriages, premature births, post partum haemorrhaging and low birth weight were found to be particularly associated with low haemoglobin concentrations during pregnancy. In Pakistan, a study of 2,500 expectant mothers suffering from anaemia during pregnancy showed a definite difference in maternal morbidity and mortality between women who had been treated for their anaemia during pregnancy, and those who had received no treatment. However, the effects on both mother and foetus of the earlier stages of iron deficiency - pre-anaemic or with moderate anaemia - are still rather unclear, although a number of recent studies have described an increased risk of prematurity in women who are iron-deficient but not anaemic.

Other effects of iron deficiency

Several recent studies have yielded evidence of varying disturbances during iron deficiency, particularly in rats : these include the synthesis of DNA, the formation of collagen, the metabolism of lipids and the maintaining of body temperature.

In all, the effects on health of iron deficiency, when it reaches the stage of anaemia, are relatively well known, although their relative importance is difficult to assess in public health terms. There is still much hesitation in the evaluation of these effects in the case of moderate iron deficiency, before it affects haematopoiesis in any way. However, recent research, especially through experimental studies on animals, provides some evidence of the possible detrimental effects of this deficiency on many metabolic functions at the tissue level.

EVALUATION OF IRON STATUS

There are different techniques for assessing the iron status of a population group. Direct measurement of iron stores using spinal taps or biopsy of the bone marrow is hardly feasible in the framework of epidemiological surveys, because of its traumatic character ; further, its interpretation is highly subjective. Different types of biological assays have been suggested for the screening of iron deficiency or the assessment of its consequences. Some have been in general use for a while, while others have only been developed recently.

Until recent years, iron deficiency was frequently identified with anaemia in nutrition studies. However, the haemoglobin concentration cannot be viewed as an excellent reflection of iron status : it is hardly specific, since anaemia may be also be caused by folic acid and/or vitamin B12 deficiency, protein-energy malnutrition, chronic infection or various blood diseases. Furthermore, the haemoglobin concentration is not a very sensitive indicator : even when anaemia is caused by iron deficiency, it reflects an advanced stage of deficiency, and only develops when the iron stores have been depleted for some time. Iron-deficiency anaemia therefore expresses the intensity of iron deficiency, but the latter may well exist before any repercussions are observable on haematopoiesis, and therefore before any detectable drop in haemoglobin concentration.

At the individual level, a number of morphological characteristics of red blood corpuscles - decreased Mean Corpuscular Volume (MCV) and Mean Corpuscular Haemoglobin Concentration - provide evidence favouring iron-deficiency as the aetiological factor in anaemia, but here too, the techniques are relatively gross, relatively unspecific and not very sensitive. MCV seems to be the most valuable of these ; table 5 shows the reference values habitually used for it.

Table 5

MEAN CORPUSCULAR VOLUME AT DIFFERENT AGES
WITH MEDIANS AND LOWER LIMITS
FOR A CONFIDENCE INTERVAL OF 95 %

Age (years)	MCV (fl or μ^3)	
	Médian	Lower limits
0.5 - 2	77	70
2 - 4	79	73
4 - 8	81	75
8 - 11	83	76
11 - 14		
Girls	85	78
Boys	84	77
14 - 18		
Girls	87	79
Boys	86	78
18 - 49		
Women	90	80
Men	90	80

Source : HERCBERG S. La carence en fer en nutrition humaine. Editions médicales internationales, Paris. 1988. 203 p.

At birth, red blood corpuscles are usually larger than those of adults. The size of the red cells declines during the first six months. During the rest of childhood, they are smaller than at any other time of life, after which they are gradually enlarged. Mean values are higher in girls than in boys after age 7, but there is no gender-related difference in adulthood.

Other biological parameters such as the assay of serum iron and the calculation of the percentage of transferrin saturation have been and still are used at both the individual and the epidemiological levels. These tests do have certain drawbacks, however : in addition to the technical problems linked with the assay methods, the significance of serum iron is limited, owing to its considerable variations in the course of the nychthemeron (1), as well as to its mediocre reproducibility. Last, the serum iron level drops during certain pathological conditions, and especially in inflammatory and infectious processes, independently of iron status. A value of less than 10 µmol/litre (or 50 mg/litre) is usually viewed as abnormal.

Assay of total iron-binding capacity (TIBC) seems to be a more reliable, as well as a more sensitive technique than determination of serum iron. It rises when iron stores decline, and is not affected by the circadian rhythm (2). It does rise in case of pregnancy, however, or of oral contraception, even when no iron deficiency is present. Values comprised between 50 and 90 µmol/l may be viewed as normal.

The percentage of transferrin saturation (ratio of serum iron/total iron-binding capacity) remains a widely used test for ascertaining the iron-deficient character of anaemia : values of less than 16 % in adults and 10 % in children under 2 are considered abnormal.

In addition to these conventional methods for assessing iron status, other more specific and more sensitive assay techniques such as quantitation of erythrocyte protoporphyrin and of serum ferritin have been developed in recent years.

Assay of erythrocyte protoporphyrin provides an indication of whether the erythrocyte precursors receive an adequate supply of iron. The erythrocyte protoporphyrin concentration rises in the blood as soon as synthesis of haemoglobin is limited by a lack of iron. This is a sensitive parameter, which is particularly valuable in epidemiological studies, since its implementation is simple and rapid. Any value exceeding 3 µg/g of haemoglobin in an individual is judged abnormal.

(1) Nychthemeron : the period of time extending over one day and one night and corresponding to a biological cycle.

(2) Circadian rhythm : the rhythm of variation, over a nychthemeron, of a biological function or constant.

In 1972, Addison et al, using a radioimmunoassay technique, discovered that minute amounts of ferritin circulate in the blood plasma. The structure of this circulating ferritin is close but not identical to that of tissue ferritin. The importance of measuring serum ferritin - the physiological role of which remains somewhat unclear - resides in the fact that its concentration varies with the state of the individual's iron stores. Studies have repeatedly demonstrated the existence of an excellent correlation between the serum or plasmal ferritin level and the extent of iron stores ; this is true regardless of the methods used to assess these stores (biopsy of bone marrow and/or liver, repeated bleeding or indirect measurement of iron absorption). This extensive research comes to the conclusion that 1 µg/l of serum ferritin is the equivalent of a reserve of some 10 mg of iron (for values below 150 µg/l) and that values of less than 12 µg/l correspond to practically non-existent stores of iron.

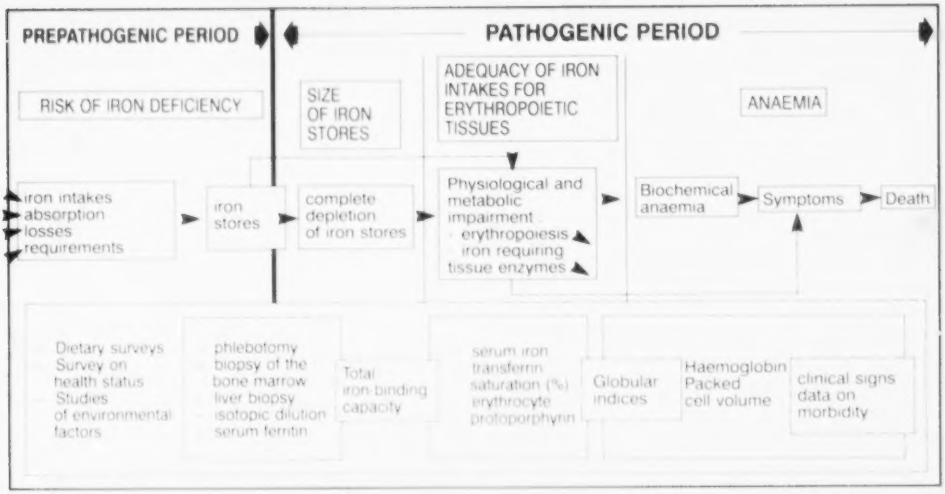
The well-known difference between men's iron stores and those of women during their reproductive years is reflected in the difference in serum ferritin concentration ; ferritinaemia is three times lower, on the average, in women. The ferritin concentration is high at birth in both sexes, and decreases during infancy. In men, the serum ferritin level rises gradually from adolescence on, whereas a similar gradual increase only occurs in women subsequent to menopause.

Quantitation of serum ferritin (be either enzyme or radio immunoassay) is sufficiently reproducible and is not affected by nyctohemeral variations. However, this parameter is no longer significant in case of liver disease, myeloproliferative syndromes, chronic inflammatory processes and cancers. Its interpretation is delicate in infants and elderly people, as well as in tropical areas in which widespread infections and inflammatory syndromes modify its significance.

Each of the biological parameters used to assess iron status reflects the changes that occur in different parts of the body at the various stages of iron depletion. Conventionally, three degrees are described, ranging from a simple negative iron balance to full-blown clinical anaemia :

- 1st degree : prelatent iron deficiency. This corresponds to the depletion of iron stores, but with no disturbance of the distribution of iron to the erythropoietic tissues ;
- 2nd degree : latent iron deficiency. There is an insufficient distribution of iron to the erythropoietic tissues, but with no modification of circulating haemoglobin ;
- 3rd degree : iron deficiency is manifest. This corresponds to iron-deficiency anaemia.

Figure 1 shows the evolution of the different haematological parameters at each degree of iron deficiency, from the prepathogenic stage to clinical anaemia.



New indicators such as intra-erythrocyte ferritin, circulating transferrin receptors, etc, seem to be exceptionally promising.

At present, authors increasingly tend to recommend the use of a combination of several biological indicators for the assessment of iron status at the population level. The models most frequently proposed define iron deficiency by the existence of at least 2 abnormal indicators out of the 3 (or 4) valid ones : serum ferritin, erythrocyte protoporphyrin, percentage of transferrin saturation (and possibly MCV). Iron-deficiency anaemia is then defined by the coexistence of iron deficiency, as defined above, and of a haemoglobin concentration located below the standards set by WHO. It is quite obvious that while this type of approach is justified for studies covering population groups, it is not applicable on the individual level in tropical areas where the clinical context (presence of a clinical picture suggestive of a disordered iron balance), awareness of the risk (the subject is a member of a population group whose physiological needs are high) and possibly assay of haemoglobin concentration, should suffice to dictate therapeutic and/or preventive action. While conjunctival pallor is strongly suggestive of anaemia, the absence of this symptom in no way precludes the existence of this condition.

Figure 1 : Natural history of iron deficiency and respective place of biological parameters for the assessment of iron status.

Source : H. DUPIN, P. GALAN, S. HERCBERG et al. (Ed.). Nutrition et Santé Publique. Approche épidémiologique et politique de prévention. Technique et Documentation (Lavoisier), Paris, 1985, 709 p.

PREVENTION OF IRON-DEFICIENCY ANAEMIA

The intensity of iron deficiency, its prevalence and its distribution within the overall population, as well as the existence of identifiable at-risk groups and the general dietary, health and environmental situation all contribute to defining the terms in which the problem of the prevention of iron-deficiency anaemia is posed. In every case, however, this prevention requires an understanding of the situation at the population level. A number of measures may be envisioned ; they may be combined, since some have short or moderately long-term effects (supplementation and fortification), while others are effective in the relatively long term, and are indispensable complementary measures.

Iron supplementation

This term is used when a nutrient is supplied in the form of a medication, administered either orally or by injection. Supplementation may be therapeutic or prophylactic. It is the preferred solution when a major deficit is present and must be improved rapidly, particularly when especially vulnerable, well-defined and attainable groups are involved (pregnant women, for instance), and when utilizable structures and logistics are available for distribution. This type of intervention is particularly appropriate for vulnerable groups, since their needs are specially high ; these include pregnant women, small children and blood donors. The effectiveness of ingestion of iron supplements by pregnant women and children has been conclusively proved. The effective dose for protecting pregnant women ranges from 45 to 120 mg of elemental iron a day, depending on the woman's iron status at the onset of pregnancy ; this supplementation should be implemented as early as is feasible, and associated, whenever possible, with folate supplementation (doses of approximately 350 µg/d). In preschool children, doses of 30 to 60 mg of elemental iron may be given. Doses of 3 to 5 mg/kg are recommended for infants. Prematures may be given similar doses starting at age 2 months.

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Iron supplementation may induce some minor side effects in certain individuals. These include diarrhoea, constipation, pyrosis, vomiting, gastric pain, blackened faeces, etc. Such reactions are usually linked to the dose ingested, and reduced if the supplement is ingested with meals.

There are a great many pharmaceutical preparations containing iron, usually corresponding to the different types of iron salts, the efficiency of which may be considered equivalent for a same dose of elemental iron.

Medications used to treat deficiency contain various types of iron salts. The percentage of elemental iron contained in the main iron salts utilized by the pharmaceutic industry is shown below (table 6).

Table 6

IRON-BASED PREPARATIONS

Iron salts	Percentage of iron
Ferrous sulfate	20
Dried ferrous sulfate	30
Anhydrous ferrous sulfate	37
Ferrous gluconate	12
Ferrous carbonate	16
Ferrous succinate	28
Ferrous fumarate	32

Source : HERCBERG S. La carence en fer en nutrition humaine. Editions médicales internationales, Paris. 1988. 203 p.

Fortification with iron

Fortification is a process by which the selected nutrient is added to foods in order to maintain or improve the diet of a specific group, a whole community or a population group. This method seems to be valuable in regions where the amount of utilisable iron contained in the traditional diet is insufficient, and does not fulfill the requirements of a large part of the population. What is difficult, here, is the definition of the food vehicle as well as of the type of iron to be used to fortify this food vehicle.

The vehicle is the foodstuff to which the nutrient is added. The characteristics of an ideal vehicle are :

— it must be consumed in sufficient amounts by the target population ;

— fortification in a relatively small number of centres must be feasible, so that the quality of the final product may be properly controlled and monitored ;

— it must be stable, regardless of storage conditions ;

— palatability (1) of the food vehicle or of other foods with which it may be combined must not be modified ;

— its cost must be acceptable.

The biochemical form of the iron used for fortification is extremely important :

— it must be easy to assimilate ; that is, its bioavailability must be satisfactory. It must be equivalent to 75 % of the bioavailability of ferrous sulfate, which is the current reference product ;

— it should not cause any undesirable modifications in the vehicle or in the food products with which the vehicle is mixed or associated ;

— it must remain stable, regardless of storage conditions.

(1) Palatability : the quality of a food which makes it taste pleasant when eaten.

Many forms of iron may be used for fortification, but few fulfill all of the requirements listed above. Ferrous sulfate, electrolytic reduced iron, iron carbonyl, ferrous ammonium citrate, orthophosphate of iron and pyrophosphate of sodium and iron are the forms of iron most commonly utilized at present. Many problems arise, owing to the difficulty of reconciling, in any one product, satisfactory assimilation, an acceptable production cost and a lack of side effects on the food vehicle. Offal haeme iron or its haemoglobin form (taken from slaughterhouse blood products, for example) has been successfully used, since it has a satisfactory coefficient of absorption.

A number of foods have been suggested as vehicles for fortification ; they include wheat flour, sugar, fish sauce, salt and baby foods. Pilot trials involving the fortification of wheat flour have been conducted on the island of Mauritius (where nutritional anaemia was the first cause of hospitalization), in Norway and in Great Britain. Most of these trials, which covered only small samples with no control group, have yielded contradictory findings which are difficult to interpret, most probably for methodological reasons. However, some industrialized countries have introduced a national programme for the fortification of wheat flour with iron. Since 1963, in Great Britain, all wheat flour contains at least 1.65 mg of iron per 100 g of flour, in the form of reduced iron or ferrous ammonium citrate. Similarly, wheat is fortified with 2.4 mg of elemental iron per 100 g in the United States. Curiously, there has been little investigation of the repercussions of these already longstanding initiatives. The doses used apparently do not suffice, however, to produce any real impact.

In Sweden, bread has been fortified with 65 mg of iron carbonyl/kg of wheat for many years now. This fortification is one of the factors responsible for the reduced level of iron deficiency observed in this country over recent decades. The impact of this particular action may be accurately assessed, since data is available for the iron status of the Swedish population at different periods : the 30 % reduction in cases of anaemia observed in Sweden over the past 20 years is attributable to this measure.

The solution consisting of fortifying wheat flour is only applicable in countries where bread or other cereal grain foods are regularly eaten by the entire population, however. This is mostly the case of the industrially developed countries, as well as of certain countries in the Near East.

Refined sugar is extensively consumed in many industrialized countries. When fortified with soluble iron, sugar undergoes little or no change in colour, even in case of prolonged storage. When added to certain substances (tea, for instance), sugar fortified with ferrous sulfate or ethylenediaminetetraacetate of iron produces a blackish colour, however ; this has something to do with the formation of tannates of iron. Its replacement by orthophosphate of iron avoids this occurrence, but iron absorption is considerably diminished.

A trial of fortification of sugar with tetraethylacetate of sodium and of iron, implemented in Guatemala, has shown this procedure to be satisfactory. Fortification of sugar is nevertheless not an ideal solution for many tropical countries, where it is not habitually consumed by the population as a whole.

Fish sauce is widely consumed in Asia, and seems to be an excellent vehicle on that continent ; the results of a pilot trial of fortification with ethylenediaminetetraacetate of sodium and of iron, conducted in Thailand, seem to be satisfactory.

Salt is universally consumed in reasonable amounts. Unfortunately, the use of soluble iron compounds affects the colour of salt, and particularly of the least refined types of salt. This colouring is accelerated by heat and humidity. A salt fortified with a mixture of ferrous sulfate, orthophosphoric acid and sodium acid sulfate recently experimented in India seems to be quite stable and correctly absorbed ; its impact on iron status is apparently satisfactory.

Baby foods containing cereal grains and iron-fortified milk seem to be the most practical products of this type for increasing the iron intake of small children in those countries where they are commonly utilized. These foodstuffs frequently contain ascorbic acid as well, thus further favouring iron absorption. In Chile, the distribution of haemoglobin-fortified biscuits at school seems to be an effective solution for school-age children.

Other iron-fortified foodstuffs such as relishes, curry, weaning cereals, etc are presently being experimented. There is probably no one ideal food vehicle. Selection should be made for each specific population group, according to dietary habits and to the structure of food production and distribution.

As for the eventuality of dangers connected with iron fortification, the problem may arise for individuals suffering from iron overload. Such people represent only a minute portion of any population, except for the Bantus, in Africa, where idiopathic haemochromatosis is frequent. From the public health viewpoint, these individuals constitute an easily controllable group. The problem should also be raised for those regions with a high prevalence of thalassaemia (countries bounding the Mediterranean), since excessive absorption may be a problem in thalassaemia patients.

Complementary measures

Along with supplementation and fortification, which may be viewed as having more or less short term effectiveness, the development of overall measures aimed at ensuring coverage of requirements through dietary iron intakes is most important. Such measures partake in the improvement of the population's general nutritional and health status :

— increasing the availability of proteins of animal origin through the development of fishing, farm-yard animal-raising and animal husbandry in countries where food products of animal origin are scarce ;

— increasing the consumption of iron-rich plant foods such as green vegetables, leafy vegetables, beans, etc. Even if their coefficient of absorption is not as high as that of the iron contained in foods of animal origin, they do represent a non-negligeable source of iron in some regions ;

— increasing the consumption of foods rich in ascorbic acid, which enhance the absorption of the iron contained in the rest of the meal ;

— improving the nutrition education of the population as a whole, and more specially, teaching it to make the most of available resources, teaching mothers to feed their children a varied diet at an early age ;

— improving the distribution of food within the family group, so that at-risk individuals (women in particular, and more specially pregnant women, and children) gain access to proteins of animal origin containing the most easily absorbable iron ; in certain communities, these "noble foods" are often preferentially reserved for men, for cultural reasons.

Another major means of combating iron-deficient anaemia is by reducing pathological losses of iron, particularly in tropical countries, through combatting parasitoses by sanitation measures and appropriate health education. Another such measure involves the recommendation of hormonal contraceptives by planned parenthood campaigns, so as to decrease menstrual bleeding, to some extent.

Last, the medical surveillance of at-risk groups, and more particularly of pregnant women, infants and children, is indispensable. This requires a better distribution of health personnel throughout each country, and especially in rural areas, the organization of antenatal consultations, information on the spacing of births and fighting of latent iron deficiency even before actual anaemia sets in.

FOLATE DEFICIENCY

FOLATE METABOLISM

Folic acid, a water-soluble group B vitamin, is formed by the association of a molecule of pterin and a molecule of para-aminobenzoic acid, to which a molecule of glutamic acid (monoglutamate) is bound by its amin radical. However, this folic acid only represents 20 to 25 % of the natural vitamin activity ; the largest part exists in the form of polyglutamates. The basal metabolic reactions in which folates play a major role are the formation of purine and pyrimidine bases, the conversion of serine into glycine, the conversion of homocystine into methionine with the help of 5-methyltetrahydrofolates, vitamin B12 and homocystine transferase. The formation of methionine is of the utmost importance for the central nervous system, since this substance is the main methylating agent in the body, and is essentially active in the methylation of choline and of adrenalin.

Last, folates are active in the conversion of uracil into thymine, which process then plays a role in the formation of DNA. It is clear that any folate deficiency has repercussions on cell division, and particularly affects those cells, such as blood cells, for which turnover is rapid.

LOSSES OF FOLATE

Folates are excreted in the urine and bile, in metabolically active and inactive forms. Approximately 100 µg of biologically active folates are excreted daily in the bile. There is an enterohepatic cycle, the role of which seems to be essential in maintaining serum folate levels. Alcohol apparently may interfere in this enterohepatic cycle. In all, folate losses may be estimated at 50 to 70 µg a day in adults.

Requirements increase considerably during pregnancy, owing to the increment in maternal erythropoiesis, as well as to foetal growth, and to storage of folates by the foetus during the terminal period of gestation. Requirements are also greater in lactating women. During children's periods of rapid growth (especially during the first year of life, and more particularly in prematures), requirements - expressed as a function of body weight - are higher than for adults.

DIETARY FOLATE INTAKES

Folic acid is a component of most natural foods (table 7), and more specifically of green vegetables, fruit, dairy products, meats, liver, yeast, etc. Folate content takes a variety of forms, ranging from monoglutamate to polyglutamates with molecules containing at least 7 glutamate radicals.

Table 7

FOLATE CONTENT OF SOME FOODS
(µg/100 g) (MAC CANCE)

Potatoes	14	Beef	7 to 17
Rice	30	Liver	100 to 200
Maize	52	Eggs	25
Tomatoes	28	Cow's milk	3 to 5
Spinach	140	Breast milk	1 to 4
Melons	30	Yeast	37
Oranges	37		

An estimated 70 % of dietary folates are actually absorbed. Mean absorption of pteroylglutamic acid is somewhere around 85 %. Polyglutamates are less well absorbed, on the other hand : conjugases, which exist both in plant and animal tissues (including in the bile and in the human intestine) are responsible for the deconjugation of polyglutamates. The action of these enzymes may be inhibited by an inappropriate pH (the optimal pH is 4.6), or by inhibiting substances contained in certain foods such as beans, yeast, as well as in some drugs (hydantoins, barbiturates and antimalarial agents). There is some possibility that oral contraceptives may counter the action of conjugase, thus hindering the absorption of folic acid.

Folates are particularly heat-labile : 50 to 95 % of the folate content of food may be destroyed by prolonged cooking. Oxidation and ultraviolet rays also inactivate folates, whence a loss of activity in case of extended storage of foods. Conservation of food, even at 4C, for 2 weeks may reduce its folate content by 20 %.

CONSEQUENCES OF FOLATE DEFICIENCY

Advanced folate deficiency is a cause of anaemia. The usual clinical picture of anaemia may be complicated by some digestive and cutaneous symptoms and in some cases, by neurological and mental disorders.

Clinical consequences

Recent research, both experimental and epidemiological, has investigated the consequences of folate deficiencies even before the stage of clinical anaemia is reached. Studies conducted by Laurence et al (1981) and by Smithells et al (1981) have led to postulation of the action of maternal folate deficiency during the periconceptional period in determining neural tube defects (especially spina bifida) and certain facial anomalies (cleft palate, harelip) in the child.

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Folate deficiency during pregnancy, with or without anaemia, also seems to be a risk factor in miscarriages and in premature delivery.

Haematological consequences

Herbert (1962) fed volunteers (including himself) a diet containing only 5 to 10 µg/d of folic acid, in order to define the successive phases of deficiency at the haematological level. These are :

— decreased serum folate activity (< 3 ng/ml on the average) at the end of approximately 3 weeks ;

— hypersegmentation of polymorphonuclears towards the 50th day ;

— abnormal urinary elimination of FIGLU (Formimonoglutamic acid) following histidine load starting at 3 months ;

— lowered erythrocyte folic acid content towards 4 months (< 150 ng/ml) ;

— medullar megaloblastosis between the 127th and the 130th day ;

— anaemia becomes patent towards the 140th day.

METHODS OF EVALUATION OF FOLATE STATUS

Macrocytosis (MCV above 95 fl) is relatively unreliable (particularly owing to possible association with iron deficiency) and occurs late : it is of some value at the population level. A drop in haemoglobin concentration is a relatively unspecific biological sign and when connected with folate deficiency it is evidence of an advanced stage of deficiency.

Quantitation of erythrocyte folates is viewed as the most sensitive test performed at the peripheral level for indicating the state of tissue folate stores. Plasmal folates tend to be more directly influenced by the amount of folates absorbed during the immediately previous period. These tests are only of value for epidemiological investigations. They are far too costly and difficult to perform to be used for individual screening.

PREVENTION OF FOLATE DEFICIENCY

The main rules of prevention, as described for iron deficiency, are also appropriate for the prophylaxis of folate deficiency.

Supplementation - systematic intake by pregnant women of 350 to 500 µg/d of folate - has yielded satisfactory results in populations in which a high prevalence of nutritional anaemia is observed in this group. Larger intakes may be required in case of severe deficiency or in women having experienced many pregnancies at short intervals.

Supplementation with folate should be associated with iron supplementation, which varies with the state of iron stores, as described in the chapter on the prevention of iron deficiency.

Most of the remarks on fortification with iron may be applied to folates. The effects of modern food processing techniques and of cooking and conservation on the folate content of foodstuffs must be given particular attention. Studies have shown the results of fortification of maize or rice with folic acid to be good, enough so to prevent anaemia in the groups studied (pregnant women). Fortified bread is not as good a food vehicle, owing to the duration of baking, which causes considerable destruction of folates.

Other measures for combating folate deficiency are based on providing information and education for the population, so as to improve use of available resources (folate-rich foods, and especially leafy vegetables...) and on a better distribution of foods, favouring those groups of individuals whose needs are greatest, along with attentive medical surveillance of at-risk groups.

CONCLUSION

The control of nutritional anaemia first requires knowledge of the prevalence of anaemia and of its distribution, as well as the identification of causal factors. The nature and severity of the deficiencies involved largely determine the choice of prevention policies. Epidemiological studies using the most appropriate biological markers contribute to a better evaluation of the situation. As in any other public health nutrition problem, the control of nutritional anaemia necessarily calls for a multisectorial approach involving both the nutrition sector and a variety of other sectors such as health, agriculture, education, etc. The existence of technical solutions tailored to fit each situation and each country should make it possible to visualize an improvement of the situation. But here again, the key to the solution of this essential public health problem resides in a combination of these specific measures and of economic and social development.

TECHNICAL NOTE

RECOMMENDED IRON INTAKES

The latest FAO/WHO expert committee has proposed figures for recommended iron intakes, taking into account bioavailability in dietary regimens around the world. The bioavailability is low in these diets (absorption of about 5 % of iron) when they are composed of cereal grains, roots and tubers, and negligeable amounts of meat or of foods rich in ascorbic acid. This is most frequently the case in developing countries, especially within the disadvantaged social categories.

Other diets have a middle-range, moderate bioavailability (absorption of about 10 % of iron), when composed essentially of cereal grains, roots and tubers, but including a reasonable amount of food rich in ascorbic acid, meat and/or fish. In some cases, bioavailability is theoretically high, but the diet contains substances such as tea or coffee which are inhibitors of iron absorption.

Last, some diets have a high bioavailability (absorption of about 15 % of iron), when food intake is diversified, with large quantities of meat, fish and foods rich in ascorbic acid. This type of diet is consumed by a large proportion of the population of industrialized countries.

The figures shown postulate that the individuals involved do not suffer from diseases susceptible of affecting their iron status.

The requirement to be fulfilled in order to avoid anaemia represents the iron intake needed so that haemoglobin concentrations will not drop below the cut-off values prescribed by WHO.

The basic requirement represents the amount of iron needed for supplying tissues normally with iron, and for the protection of all clinically detectable functions.

The proposed figures, which take into account the variability of requirements, represent the safe levels of intake covering those requirements for 95 % of the population of a given age and sex.

ESTIMATED DIETARY IRON REQUIREMENTS [1]

DIET WITH LOW BIOAVAILABILITY (5 %)

Group	Age	Requirements to be covered to avoid anemia [2]		Basic requirements	
		Median value	Including variability [4]	Median value	Including value [4]
Infants	0-3 months	—	—	—	—
	3-12 months	11	14	17	21
Children	1-2 years	6.5	8	10	12
	2-6 years	7.5	9	11	14
	6 -12 years	12.5	16	19	23
Boys	12-16 years	19	24	29	36
Girls	12-16 years	22	27	32	40
Men	+ 16 years	12	15	18	23
Women					
menstruating		17	(29) [4]	(25) [3]	(48) [3]
post-menopausal		10	13	15	19
pregnant [3]		—	—	—	—
lactating		14	17	21	26

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DIET WITH MODERATE BIOAVAILABILITY (10 %)

Group	Age	Requiremens to be covered to avoid anemia [2]		Basic requirements	
		Median value	Including variability [4]	Median value	Including variability [4]
Infants	0-3 months	—	—	—	—
	3-12 months	5.5	7	8.5	11
Children	1-2 years	3.5	4	5	6
	2-6 years	3.5	5	5.5	7
	6 -12 years	6	8	9.5	12
Boys	12-16 years	9.5	12	15	18
Girls	12-16 years	11	13	16	20
Men	+ 16 years	6	8	9	11
Women					
menstruating		8	14	12.5	(24) [3]
post-menopausal		6.5	6	9.5	9
pregnant [3]		—	—	—	—
lactating		7	9	10.5	13

DIET WITH HIGH BIODISPONIBILITY (15 %)

Group	Age	Requirements to be covered to avoid anaemia[2]		Basic requirements	
		Median Value	Including variability[4]	Median Value	Including variability[4]
Infants	0-3 months	—	—	—	—
	3-12 months	3.8	5	5.5	7
Children	1-2 years	2.2	3	3.3	4
	2-6 years	2.5	3	3.7	5
	6 -12 years	4.2	5	6.3	8
Boys	12-16 years	6.5	8	9.7	12
Girls	12-16 years	7.3	9	10.8	13
Men	+ 16 years	4.1	5	6.1	8
Women					
menstruating		5.6	10	8.3	16
post-menopausal		3.4	4	5.1	6
pregnant[3]		—	—	—	—
lactating		4.7	6	7	9

(1) Storage requirements for iron have not been calculated. They may be some 50 % higher than the above-mentioned basic requirements. Requirements have been calculated on the base of estimated bioavailability in adults. Requirements for infants and children may possibly be overestimated if their absorption is more efficient, as seems to be indicated by some studies.

(2) Amounts sufficient for avoiding the development of clinical anaemia. This may be an acceptable objective in many situations.

(3) The values in parentheses represent intake levels judged improbable for the usual dietary regimens.

(4) The variability of individual requirements is taken into consideration. The figure is determined so as to cover the needs of 95 % of individuals in each age group and sex.

Taken from FAO/WHO. Requirements of vitamin A, iron, folate and vitamin B12. FAO Series : Food and nutrition. Rome, 1989. N.23. 119 p.

IVACG RELEASES STATEMENT ON ROLE OF VITAMIN A IN CHILD HEALTH AND SURVIVAL

The XIII International Vitamin A Consultative Group (IVACG) Meeting in November 1989 reviewed the evidence available to date on the relationship of vitamin A depletion and deficiency to childhood morbidity and mortality. Results from completed studies as well as preliminary findings of others underway were presented and discussed by experts from several disciplines. The IVACG Steering Committee realized the need for an interim statement summarizing the weight of evidence available because results from several large, randomized masked trials are unlikely to be available for one to two years. The following statement represents the steering committee's careful consideration of the available evidence.

An adequate vitamin A status prevents nutritional blindness and contributes significantly to child health and survival.

The role of vitamin A in preventing nutritional blindness is well documented.

Evidence is accumulating that it also reduces mortality. The mechanism(s) by which it has this effect is unclear.

The impact of improved vitamin A nutrition will vary with the severity of vitamin A deficiency and the contributions of other ecological factors.

It is therefore imperative to improve the diet and raise the level of vitamin A nutrition where a current intake is inadequate.

The IVACG Steering Committee hopes that this statement will be useful in the process of formulating country and regional policies and programs to control and combat vitamin A deficiency.

The International Vitamin A Consultative Group was established in 1975 to guide international activities aimed at reducing vitamin A deficiency in the world.

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Much scientific research is currently under way on the prevention of iron-deficiency.

In an issue of the "Food and Nutrition Bulletin", Martinez-Torres, P. Taylor, I. Leets et al.*, review a number of studies on the bioavailability of iron. One of them analysed 4 types of maize bread : whole maize, Mexican tortillas, pancakes made of maize with the pericarp removed and pancakes made of precooked maize flour.

Four typical breakfasts served in various regions of Venezuela, Sao Paulo and Lima, Santiago da Chile and Salta, in Argentina, were also tested.

Last, 2 standard meals, one composed essentially rice of black beans and maize bread, the other including beef, rice, black beans and maize bread were analysed to determine the bioavailability of their iron content, following modification of the type of maize flour (whole or precooked) used to make the bread eaten with these meals.

These tests were performed in vivo on healthy, volunteer Venezuelan adults following consumption of meals containing marked 55iron or 59iron. The reference dose contained 3mg of iron in the form of ferrous sulfate, with a 2 : 1 molar ascorbate:iron ratio.

276 individuals were tested with whole maize bread. Iron absorption was 1.2 to 2.3 % for subjects whose absorption of the reference dose of iron was below 35 %. When the latter was above that figure, the coefficient of iron absorption from maize bread rose sharply to 4.5 %. For maize-based breads, the iron absorption coefficient ranges from 2.8 to 6.7 %. It is highest for precooked maize pancakes and lowest for whole maize tortillas. There is a converse relationship between phytate content and coefficient of iron absorption.

201 individuals were tested for 4 breakfasts. Findings were broken down by type of breakfast and degree of iron deficiency. This showed absorption coefficients ranging from 0.8 to 3.5 % for non-deficient subjects, from 2.7 to 6.5 % in the moderately deficient and from 2.7 to 10 % for severely deficient subjects.

The iron absorption coefficient of a basic breakfast containing bread made of precooked flour was 6.3 %, for the dozen adults studied. The addition of one or two eggs brings coefficients down to 4.5 % and 4.9 %. If 15 or 30mg of ascorbic acid are added to the basic breakfast, coefficients are 6.9 % and 21 %. In terms of amounts of iron actually absorbed, it is or course necessary to take into account the actual iron content (haeminic and non-haeminic iron) of the food eaten.

Last, the coefficients of iron absorption of Latin American meals accompanied by different types of breads are relatively similar despite varied phytate and tannate contents. The figures are 2.7 %, 2.8 %, 6.4 % and 3.5 %. Only the meal with a low phytate content and including meat had a significantly higher coefficient.

These results seem to indicate that increased iron absorption in the case of iron deficiency is stimulated by a decrease in iron reserves, but is independent of the seriousness of the deficiency. Furthermore, although the coefficient of absorption is higher for bread made of precooked flour (low in phytates) than for bread made with whole flour, the total amount of iron absorbed is not very different, since processing of the kernel removes much of its iron content.

* *Iron absorption from maize bread. In : Food and Nutrition Bulletin (UNU/WHP). 1987, 9, n 4, pp 62-69.*

The authors draw 3 practical conclusions :

- breads made of precooked flour are preferable, but should be accompanied by iron-rich foods ;
- choice of a beverage to accompany breakfasts should consider the major inhibiting effect of tea on the absorption of iron, and the lesser inhibiting effect of coffee (which also contains tannates) ;
- ascorbic acid favours iron absorption, but a sufficient amount must be provided for the effect to be produced.

An other study, conducted by P. Vijayalaksjhmi, U. Kupputhai and V. Uma Maheswari *, covered 30 anaemic adult women and 30 non-anaemic control women. The former were given 120mg of ferrous sulfate daily during 90 days, and the non-anaemic women were given a placebo.

On days 0 and 90, haemoglobin, serum iron, total iron-binding capacity and haematocrit were assayed. Pulse and blood pressure were taken before and after various activities on days 0 and 90. Vital capacity and basal metabolism were also assessed. The ability to perform certain physical activities connected with farming was measured on days 0 and 90.

Supplementation had a positive impact on the blood indicators (the Hb level rose from 9.4 to 12.9, as well as on the pulse, blood pressure and vital capacity of the anaemic women.

When compared to the anaemic women, on day 0, non-anaemic women showed better performances. The former performed significantly better following supplementation than on day 0.

38 Although no statistical comparison was made between this group and that of non-anaemic women, the general impression is that their performance, following supplementation, still remained inferior to that of non-anaemic women.

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* Anaemia and work output of farm women. In : The Indian Journal of Nutrition and Dietetics. 1987, 24, n 9, Sept., pp. 253-259.

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IRON AND FOLATE - DEFICIENCY ANAEMIAS

1980 - N° 186

Nutritional anaemia, a serious nutrition and public health problem in the developing countries, is also present in the industrialized countries, although to a lesser extent. The presence of nutritional anaemia is indicative of an already advanced stage of iron and/or folate deficiency. This means that prevalences of earlier stages of these deficiencies, defined by depletion of iron stores, are much higher still.

It is now possible to determine the iron status of supposedly healthy population groups, using several reliable biochemical indicators : this yields information on the evolution of this condition, from the decline in iron stores to an advanced stage of iron-deficiency anaemia.

Of all human nutritional requirements, the need for iron is one of those for which coverage raises the greatest practical problems. There is, ordinarily, an imbalance between losses of iron and the very small proportion of dietary iron which is easily absorbable by the human body, and this imbalance is even more marked in young children, women of childbearing age and pregnant women.

Thanks to this better epidemiological understanding, derived from knowledge of iron status, more appropriate preventive measures may be implemented and their impact evaluated with greater accuracy. The work done in this field by the INACG/WHO team is a most valuable aid in guiding public health policies as well as reflection on prevention.

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